



PATENT APPLICATION

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants:

Ammons et al.

Serial No.: 08/232,527

Filed: April 22, 1994

For: Method of Treating Conditions
Associated With Intestinal
Ischemia/Reperfusion

Group Art Unit: 1815

Examiner: Sayala, C.

) I hereby certify that this paper is being
) deposited with the United States Postal
) Service as First Class mail, postage
) prepaid, in an envelope addressed to:
) Assistant Commissioner for Patents,
) Washington, D.C. 20231, on this date.

August 24, 1995

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Registration No. 31,879

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DECLARATION OF WILLIAM STEVE AMMONS UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

WILLIAM STEVE AMMONS DECLARES AND STATES THAT:

1. I am an inventor of the subject matter claimed in the above-identified patent application (hereinafter the "patent application"). I make this declaration for purposes of responding to issues raised in the Office Action of February 24, 1995.

2. That my educational background and work experience are as follows:

I am Director, Department of Pharmacology, at XOMA Corporation, with responsibility for pharmacological and pharmacokinetic studies of XOMA products. I have a

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B.A. in biology from University of North Carolina and a Ph.D. in physiology from Emory University. I received post doctoral training for three years followed by one year as Research Assistant Professor in the Department of Physiology and Biophysics, University of Oklahoma Health Services Center. I continued my academic career for seven years in the Department of Physiology at Jefferson Medical College, Thomas Jefferson University, as Assistant Professor and Associate Professor. I joined XOMA Corporation as a Group Leader in the Department of Pharmacology/Toxicology, and after two years, became Director of The Department of Pharmacology.

3. That I am knowledgeable about bactericidal/permeability-increasing protein products (BPI) and the biological effects thereof. I have expertise in animal physiology and pharmacology and have supervised groups at XOMA responsible for developing models of sepsis and shock, including models of endotoxemia and bacteria, in multiple animal species. As a part of these efforts, I have conducted mortality studies, physiological studies of the cardiovascular system, organ failure studies, studies to analyze changes in cytokine levels and in metabolism and coagulation factors. Recent efforts have included development of models of ischemia/reperfusion injury. As a part of Phase I clinical trials, I have supervised human pharmacokinetic studies. I have participated in the preparation of 3 INDs and have presented pharmacology and toxicology data to the FDA. I am a member of the American Physiological Society, Society for Neuroscience, American Heart Association, International Association for the Study of Pain and Shock Society. I have published approximately 50 journal articles and book chapters in the areas of physiology, pharmacology and toxicology.

4. That intestinal ischemia/reperfusion is a condition initiated by deprivation of the intestine of oxygenated blood (ischemia) followed by the reintroduction of blood flow (reperfusion).

5. That a variety of non-endotoxin factors have been implicated in intestinal ischemia/reperfusion injury as shown in references attached as Appendices 1-25 to this Declaration. These factors include cells, such as neutrophils and platelets, and numerous mediators released from cells, including free oxygen radicals, histamine, prostanoids, leukotrienes and platelet-activating factor (PAF).

6. That although a role for endotoxin has been suggested in intestinal ischemia/reperfusion injury, little evidence supported that hypothesis.

7. That intestinal ischemia/reperfusion results in a number of adverse physiological effects, as described in Example 1 of the patent application, that include bradycardia, respiratory depression, arrhythmias and hypotension.

8. That the adverse physiological effects of bradycardia, respiratory depression and arrhythmias, described in Example 1 of the patent application as associated with intestinal ischemia/reperfusion, are not adverse effects of sepsis. In fact, the opposite effects of tachycardia and increased respiration are associated with sepsis (see, e.g., review of Gram-Negative Sepsis by Bone, attached as Appendix 26 to this Declaration).

9. That the effects of BPI, as demonstrated in Example 1 of the patent application, on bradycardia, respiratory depression, arrhythmias and hypotension were unexpected, and particularly surprising was BPI's effect on arrhythmias in intestinal ischemia/reperfusion.

10. That the conditions associated with partial hepatectomy (Boermeester et al.), hemorrhagic shock (Yao et al. and Bahrami et al.) or endotoxin infection and endotoxemia (WO92/09621; WO92/03535; WO93/06228; U.S. Patent Nos. 5,089,274; 5,171,739; 5,334,584; 5,308,834; and 5,234,912; Mainous et al. and Gathiram et al.), are not the same conditions as intestinal ischemia/reperfusion.

11. That BPI was surprisingly effective in alleviating the adverse physiological effects of intestinal ischemia/reperfusion.

12. I declare further that all statements made herein of my own knowledge are true and all statements made herein on information and belief are believed to be true, and all these statements are made with the knowledge and understanding that willful false statements and the like are punishable by fine, or imprisonment, or both, as set forth in 18 U.S.C. 1001, and that such false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

8/24/95
DATE


William Steve Ammons